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(54) Title: THERAPEUTIC PREPARATION FROM COFFEE BEAN AND METHOD FOR PRODUCING

(57) Abstract: A raw green coffee bean extraction method and coffee extract end product. The method produces a coffee extract end product which contains antioxidants (phenolic compounds), diterpenes (having detoxification properties), has greater bioavailability and greater ability to quench oxidative stress in comparison existing polyphenol extracts.

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"THERAPEUTIC PREPARATION FROM COFFEE BEAN AND METHOD FOR PRODUCING"

BACKGROUND OF THE INVENTION

1. Field of The Invention

The present invention relates to the use of an extract derived from green coffee beans, for the purpose of consumption as a dietary supplement or other functional food, as a preservative, or for cosmetic purposes.

2. Background Information

This invention relates to a new coffee bean extract. The resulting extract can then be encapsulated, tableted, or placed in any other type of acceptable pharmaceutical carrier for consumption by humans or animals as a dietary supplement or other functional food. The extract can also be used as a preservative or as a topical skin treatment in cosmetic or pharmaceutical preparations.

The resulting extract will be a source of phenolic compounds, which are known antioxidants and anti-tumor agents. Phenolic acids in coffee are mainly esters of quinic acid with different amount of caffeyl groups attached to its different positions. The phenolic acids present in coffee such as chlorogenic acid, caffeic acid, para-coumaric acid and eugenol have been shown to exert cancer preventive activities in animal models. Chlorogenic acid has also been found to inhibit methylazoxymethanol-induced large intestinal tumors in hamster models.

Chlorogenic acid, which is the main phenolic acid in coffee, is able to protect the gastric mucosa against irritations, and, therefore, improves the digestibility of foods, beverages and medicaments. The improved digestibility is expressed through a much-reduced systemic acid secretion (such as causes heartburn, etc.), which has been found to be directly dependent on an increased level of chlorogenic acid content in raw green coffee beans.

Chlorogenic acid, an ester of caffeic acid and quinic acid, is an antioxidant in vitro and might therefore contribute to the prevention of cardiovascular disease. In vivo assays show that one third of chlorogenic acid and almost all caffeic acid is absorbed in the small intestine of humans. This implies that part of the chlorogenic acid from foods will enter into the blood circulation, but most will reach the colon. Caffeic seems to be more bioavailable. (Olthof et al J Nutr 2001 Jan;131 (1):66-71).

Chlorogenic acid has a chemopreventative effect on rat stomach cancer. (J Toxicol Sci 1999 Dec;24(5):433-9 Shimizu et al).

Normally the natural chlorogenic acid content of coffee is reduced by approximately 40 to 80% during conventional roasting process. Analysis by the present inventor indicates that green coffee beans which initially contain 4% phenolic acids contain, respectively, 2% phenolic acids when light roasted, 1% when medium roasted, and less than 0.5% when dark roasted. This clearly represents a significant loss of beneficial compounds. Thus, the use of a green coffee bean extract will result in a product which preserves the concentrations of phenolic compounds in green coffee beans.

The resulting extract will also be a source of beneficial compounds such as polyphenols and diterpenes, which have detoxification properties in humans, as well as other beneficial compounds such as triterpenes.

SUMMARY OF THE INVENTION

In view of the foregoing, it is an object of the present invention to provide a green coffee bean extract.

It is another object of the present invention to provide a novel, extract, which may be used as a dietary supplement, flavoring, or functional food containing an extract of green coffee beans which contains polyphenolic acids and other beneficial compounds, such as diterpenes.

It is another object of the present invention to provide an extract of polyphenolic acids and other beneficial compounds which are healthier than existing polyphenol extracts.

It is another object of the present invention to provide an improved extract which is more bioavailable than polyphenol extracts which are processed by conventional methods.

It is another object of the present invention to provide an improved extract which can be utilized as preservative in beverages and foodstuffs.

It is another object of the present invention to provide an improved extract which can be utilized as preservative in beverages and foodstuffs.

It is another object of the present invention to provide an improved extract which can be utilized for the purposes of quenching free radical and relieving oxidative stress in mammal and humans.

It is another object of the present invention to provide an improved extract which can be utilized for preventing the initiation or promotion of carcinogenesis and tumorigenesis.

It is another object of the present invention to provide an improved extract which

can be utilized for increasing the subject longevity or the promotion of healthier diet.

It is another object of the present invention to provide an improved extract which can be utilized for preventing or reducing the risk of cardiovascular heart disease.

It is another object of the present invention to provide an improved extract which has greater ability to quench oxidative stress and destroy free radicals than polyphenol extracts which are processed by conventional methods.

It is another object of the present invention to provide an improved raw green coffee bean extract which yields a more healthful end product than existing polyphenol extracts.

It is another object of the present invention to provide a new method for producing phenolic compound rich preparations.

It is another object of the present invention to provide a new method for producing more phenolic compound rich preparations than conventional methods produce.

It is another object of the present invention to provide a new method for producing phenolic compound rich preparations with constituents which, while obtainable from alternative sources, are present in more beneficial quantities or ratios than are presently available through conventional source materials or through practice of conventional processes.

It is another object of the present invention to provide a new method for producing phenolic compound rich preparations from source materials not heretofore recognized as a practical source of such compounds.

In satisfaction of these and related objects, the present invention provides a novel and unobvious raw green coffee bean processing method and extract end product.

Remarkably, this simple method of the present invention produces an extract product which is more bioavailable, contains a healthier profile of antioxidants (phenolic compounds) and more diterpenes (having detoxification properties).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The new extract of the preferred mode of the present invention is the product of extracting the beneficial compounds out of raw green coffee beans. This is a significant departure from conventional production of polyphenol extracting methods, where green tea is the sole source of the end product, whereas the end product of the present invention achieves a chemical profile of phenolic acids and other beneficial compounds which is different from existing polyphenol extracts. This new process yield more active, more bioavailable, and larger quantities of phenolic compounds than those found in existing polyphenol extracts processed from the extraction of green tea leaves, grape seeds or other polyphenol containing compounds.

Raw green beans of any origin are ground in a commercial grinder to a very fine powder. (less than 0.63mm). The grinding of the beans to a fine consistency increases the surface area of each bean which in turn benefits the extraction process by increasing yield of phenolic compounds and other beneficial compounds. AOAC Official Methods of Analysis says to grind green coffee to pass through a number 40 sieve. Both methods recommend keeping the coffee very cold to avoid pastiness. Typically, in production, a desired extract is selected and prepared based upon the positive effects it is reported to impart. The extraction and concentrations may be performed by any method well known in the relevant art of making concentrated extracts from natural products such as water, alcohol, and solvent based extractions with accompanying concentration of the extracted

material. Additionally,

As an example the present invention employs a 60% methanol/water extraction, a butanol/water extraction as well as a supercritical extraction technique. For comparison, Green tea is historically extracted with ethanol/water. The supernate is then decanted using the AOAC method which dries down the residue and then boils it prior to polyphenol analysis. Other drying methods that can be used, but are not limited to, include vacuum filtration, spray drying and evaporation. The beans may be extracted more than once to enhance the process.

The beans may also be decaffeinated and put through other purification steps such as gel permeation, preparative HPLC or nanofiltration Solvents and adsorbents currently used to decaffeinate beans include but are not limited to: dichloromethane, ethyl acetate, edible fats and oils, CO2 and acid activated carbon. Extracts can also be decaffeinated using liquid-liquid extraction with di-chloromethane. Decaffeination can also be achieved without an organic solvent "water decaffeination".

High performance liquid chromatography analysis (HPLC) indicates the total chlorogenic acid content of green arabica beans at about 6.9%, Robusta beans are at about 10%. A number of different chlorogenic acids are present, 5-caffeoylquinic acid is present in the largest amount. Dicaffeoyl and feruloyl quinnic acids are also present together with eht 3 and 4- isomers of monocaffeoylquinic acid.

Green coffee beans contain about 1.3% diterpenes in arabica and 0.2% diterpenes in green robusta. The diterpenes are cafestol and kahweol. Various sterols and tocopherols are also present in the lipid part of green beans. The presence of alkanoylated 5-hydroxytryptamines in the wax on the outer surface of the green beans are present at 500-1000mg/kg.

Trigonelline is present at 1.1% is arabica and 0.65% in robusta. Trigonelline is transformed somewhat into nicotinic acid.

Apart from chlorogenic acids the main acids present in significant quantities are quinic, malic, citric, lactic, pyruvic, succinic and glycolic.

The extract may also be derived from ground roasted beans or brewed coffee extracts derived from raw beans, or roasted beans of varying degree (the less roasted-the more polypohenols remain).

During any of the roasting methods described above (or upon using variations thereof), the extract may be flavored or supplemented with desired additives by conventional methods.

The invented procedures can also be used for producing decaffeinated or partly decaffeinated raw green coffee bean extracts, in that a raw coffee is used as a basis and then the caffeine is partly or totally removed therefrom.

In the preceding examples, all percentages are reported by weight. The chlorogenic acid an other contents given were obtained by high-pressure liquid chromatography (HPLC) and UV photometric methods.

EXAMPLE 1

Antioxidant Analysis of Coffee Beans

100 g of Columbian green coffee beans was placed into glass boiling bottle (1 liter) containing 300 ml of water, water-bath heating at 75°C for 2.5 hours, filtered the water extract out, The bottle was added 200 ml of water and heated at 75°C for 1 hours, filtered the second water extract out, and repeating this to get the third water extract. The three water extracts were combined and evaporated by rotary evaporator at 55°C under

reduced pressure to get 200 ml of total water extract. Two 200 ml of chloroform were used to remove impurities from the 200 ml of water extract by two phase partition. The chloroform-extracted water extract was extracted by 200 ml of butanol 4 times. The combined butanol extract was evaporated by rotary evaporator under reduced pressure at 50°C. The residue was dissolved in 75 ml of water and freeze-drying was performed, and 14 grams of purified green coffee bean polyphenols was obtained. The yield is 14% (w/w). HPLC analysis as depicted in Figs 1 – 3 demonstrate that the extract contains 42% (w/w) of known coffee polyphenols. Specific compounds indicated on the HPLC were:

Lipophilic Antioxidants of Green Coffee Beans:

2,3,5-TRIMETHYLPHENOL,

2-ETHYLPHENOL ,

2-METHOXY-4-ETHYLPHENOL

24-METHYLENE-CYCLOARTENOL

24-METHYLENEPHENOL

4-ETHYLPHENOL

4-METHOXY-4-VINYLPHENOL

ACETALDEHYDE

ALPHA-TOCOPHEROL

BETA-TOCOPHEROL

EUGENOL (0.5%)

ISOEUGENOL

LINOLENIC-ACID (5%)

O-CRESOL

O-XYLENOL

P-COUMARIC-ACID

P-CRESOL

Ferulic acid (0.02%)

Isoferulic acid

Hydrophilic Antioxidants of Green Coffee Beans:

3,4-DICAFFEOYL-QUINIC-ACID

3,5-DICAFFEOYL-QUINIC-ACID

4,5-DICAFFEOYL-QUINIC-ACID

(above 3 acids are about 2% in green coffee beans)

CAFFEIC ACID (0.01%)

CHLOROGENIC-ACID (6%)

EXAMPLE 2

Variations of Extraction Protocols

Example 2A

200 g of Columbian green coffee beans was placed into glass boiling bottle (1 liter) containing 600 ml of water, water-bath heating at 75°C for 2.5 hours, filtered the water extract out, The bottle was added 400 ml of water and heated at 75°C for 1 hours, filtered the second water extract out, and repeating this to get the third water extract. The three water extracts were combined and evaporated by rotary evaporator at 55°C under reduced pressure to get 400 ml of total water extract. Two 300 ml of chloroform were used to remove impurities from the 400 ml of water extract by two phase partition. The chloroform-extracted water extract was extracted by 300 ml of butanol 4 times. The

combined butanol extract was evaporated by rotary evaporator under reduced pressure at 50°C. The residue was dissolved in 100 ml of water and freeze-drying was performed, and 26 grams of lightly yellowish white purified green coffee bean polyphenols was obtained. The yield is 13% (w/w). HPLC analysis showed that the extract contains 41% (w/w) of known coffee polyphenols.

Example 2B

300 g of Columbian green coffee beans was placed into glass boiling bottle (1 liter) containing 700 ml of water, water-bath heating at 75°C for 2.5 hours, filtered the water extract out, The bottle was added 300 ml of water and heated at 75°C for 1 hours, filtered the second water extract out, and repeating this to get the third water extract. The three water extracts were combined and evaporated by rotary evaporator at 55°C under reduced pressure to get 400 ml of total water extract. Two 400 ml of chloroform were used to remove impurities from the 400 ml of water extract by two phase partition. The chloroform-extracted water extract was extracted by 400 ml of butanol 4 times. The combined butanol extract was evaporated by rotary evaporator under reduced pressure at 50°C. The residue was dissolved in 150 ml of water and freeze-drying was performed, and 44 grams of purified green coffee bean polyphenols was obtained. The yield is 14.6% (w/w). HPLC analysis showed that the extract contains 40% (w/w) of known coffee polyphenols.

Example 2C

Green beans are ground and extracted with a ratio of water and an alcohol (ratio between 40% to 90% alcohol where alcohol can be any alcohol such as ethanol, methanol, or

butanol. Green bean extract is dried through spray drying or freeze drying. Extract is assayed by HPLC and should have at least 15% antioxidant content as determined by the amount of three primary chlorogenic acid components.

Example 2D

Green beans are ground and extracted with a ratio of water and and alcohol and further extracted with chloroform. Extract is dried and assayed for phenolic compounds by HPLC and is found to have at least 25% antioxidant content as determined by the amount of the primary chologenic acids. This extract may end up being low or void of caffeine*.

Example 2E

Green beans are ground and extracted with SCF and subsequently extracted with 60% ethanol/water mixture. Resulting extract is dried and assayed for phenolic compounds by HPLC and is found to have at least 25% antioxidant content as determined by the three major chlorogenic acids.

Example 2F

Green Beans are ground and extracted using super critical fluid extraction. The extract is spray dried or freeze dried and assayed by HPLC for identifiable organic compounds such as eugenol and furulic acid and assayed for antioxidant activity. Figure 4 already submitted shows the antioxidant activity as determined by linoleic acid autoxidation assay for two of the most active SCF fractions.

EXAMPLE 3

Antioxidant Activity

The methodology used to measure antioxidant activity in the present invention was the Linoleic Acid Autoxidation method is a rapid screening test to determine antioxidant potencies of natural and synthetic antioxidants. It measures antioxidant efficiencies in a model system consisting of micelles of sodium dodecyl sulfate (SDS) with added linoleic acid. The method involves following the development of absorption at 234 nm which results when linoleic acid is oxidized to its conjugated diene hydroperoxide by the addition of the compound ABAP (2,2'-azobis (2-amidinopropane) dihydrochloride), the initiator. The antioxidant efficiency (the rate constant for the reaction of the peroxyl radical from linoleic acid with the antioxidant divided by the propagation rate constant for autoxidation of linoleic acid) of the test substance is compared to that of alpha tocopherol. Then absolute value of the rate constant for the reaction of alpha tocopherol with peroxyl radicals is known in micellar systems. Figures 4 and 5 shows the Linoleic Acid Autoxidation and inhibition by green tea and green coffee beans.

The extract from the preceding examples can then be encapsulated, tableted, or otherwise placed in an approved pharmaceutical carrier. The resulting extract can be taken as a dietary supplement or functional food by a human or other mammal, by being administered an amount of the extract and the composition containing, in addition to the extract, an orally administrable pharmaceutical vehicle or other food product.

The preceding example illustrates that a more healthful polyphenol extract product can be produced by a very simple variation of conventional polyphenol extraction methods. In addition, an end product which is healthier and cheaper than existing polyphenol extracts can be produced, and thereby provide an economic

benefit to vendors. The present method yields a product which is in no way undesirable from an aesthetic standpoint. Thus, there is no reason not to, and every reason to, adopt the present coffee extraction processing methods for the well being of consumers.

EXAMPLE 4

Preservation of Beer

EXAMPLE 4A

3.3 lb light malted extract was boiled for 10 minutes, filtered and introduced into fermentation tank together with 1 cup of sugar. 10 gram of hops containing 9% of alpha acids was boiled for 45 minutes, filtered and put into fermentation tank as bitterness hopes. Another 7 gram of hops containing 4.5% of alpha acids was boiled for 5 minutes, filtered and put into fermentation tank as aroma hops. Put more water into fermentation tank till 4 gallons mark, cool the whole liquid to room temperature and 5 gram dry beer yeast was introduced into fermentation tank. After 10 days of fermentation. The beer was cooled to 0 C and filtered.

EXAMPLE 4B

3.3 lb light malted extract and 300 grams of green coffee bean powder were put into water, boiled for 10 minutes, filtered and introduced into fermentation tank together with 1 cup of sugar. 10 gram of hops containing 7.5% of alpha acids was boiled for 45 minutes, filtered and put into fermentation tank as bitterness hopes. Another 7 gram of hops containing 5% of alpha acids was boiled for 5 minutes, filtered and put into

fermentation tank as aroma hops. Put more water into fermentation tank till 4 gallons mark, cool the whole liquid to room temperature and 5 gram dry beer yeast was introduced into fermentation tank. After 10 days of fermentation, the beer was cooled to 0 C and filtered.

Example 4C

2 lb pale malted extract was boiled for 10 minutes, filtered and introduced into fermentation tank. 5 gram of hops containing 8% of alpha acids was boiled for 45 minutes, filtered and put into fermentation tank as bitterness hopes. Another 3 gram of hops containing 5.6% of alpha acids was boiled for 10 minutes, filtered and put into fermentation tank as aroma hops. Put more water into fermentation tank till 2 gallons mark, cool the whole liquid to room temperature and 3 gram dry beer yeast was introduced into fermentation tank. After 8 days of fermentation, 25 grams of purified GCBP was added into fermentation tank. The fermentation was continued for 2 more days. The beer was cooled to 0 C and filtered.

Example 4D

2 lb amber malted extract was boiled for 10 minutes, filtered and introduced into fermentation tank. 5 gram of hops containing 9% of alpha acids was boiled for 45 minutes, filtered and put into fermentation tank as bitterness hopes. Another 3 gram of hops containing 5.2% of alpha acids was boiled for 5 minutes, filtered and put into fermentation tank as aroma hops. Put more water into fermentation tank till 2 gallons mark, cool the whole liquid to room temperature and 3 gram dry beer yeast was introduced into fermentation tank. After 7 days of fermentation, 10 grams of GCBP

was added into fermentation tank. The fermentation was continued for 3 more days. The beer was cooled to 0°C and filtered.

The beers obtained from above 4 samples were checked and analyzed. The results were as shown in FIGURE 6.

EXAMPLE 5

ANTI-AGING

Green Beans are ground and extracted with 60% ethanol/water and freeze dried . Extract is employed in Caenorhabditis elegans Life-span assay (Reference Johnson, Thomas et.al, Proc. Natl. Acad. Sci. Vol 79, pp 6603-6607, November 1982. Genetics). Essentialy, C. elegan worms are allowed to grow on agar plates until synchronous aging populations are determined and worms can be then transferred thrice weekly onto new agar until all worms have died. Agar is prepared with and without above described green coffee extract. At each transfer of survival populations, the numbers of worms alive, dead, or lost were recorded. Life expectancy of the worms that were living in media enhanced with a 13% polyphenol green bean extract (RJR in the figure) went up 3.5 to 5.5 days above those without the enhancement. See Figure 7.

EXAMPLE 6

BIOAVAILABILITY

Evidence exists to support the increase in bioavailability and absorption of the phenolic compounds of the green coffee bean relative to the current phenols available

today such as green tea extracts or grape seed extracts. It has been show that the type of phenolic compound is important to its solubility and stability when ingested into mammal subjects. For example, grape seed extracts containing high levels of pro-anthocyanidin polyphenols have a low solubility and therefore limit the amount of absorption in the body. Green tea extracts have a high level of catechin polyphenols whereas green coffee beans have a high level of chlorogenic acids. To explore the bioavailability effectiveness of these polyphenols both of these extracted ingredients were evaluated in mammal subjects.

To understand the relationship between tea consumption and its biological effects a study was conducted by Kim S, et al as published in the Nutr Cancer 2000 volume 37 titled "Plasma and tissue levels of tea catechins in rats and mice during chronic consumption of green tea polyphenols to measure the catechin levels during and after oral consumption of green tea extracts. Plasma and tissue levels of (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), and (-)-epicatechin (EC) were measure after the subjects were given an oral dosage of green tea polyphenol preparations. Dosages are as follows:

A) Humans ingested 1.5 grams decaffeinated green tea solids

B) Sprague-Dawley male rats received decaffeinated green tea at 9 mg solids/mg for 3 weeks

C) SKH-1 female mice received regular green tea at 9 mg solids / ml for 6 weeks.

Plasma concentration data is indicated in the chart of FIGURE 8.

Green tea solids have a catechin level of close to 20%. Therefore at a dosage of 1.5 grams per day of solids the level of total catechins is equivalent to .3 grams. The total catechin level measured in the human plasma samples, for example,

indicates a peak concentration of .48 mg. One can easily determine the bioavailability at 0.16%, yielding a significantly low level readily absorbed by human subjects. To understand the stability and bioavailability of chlorogenic acid, the major antioxidants in garland (Chrysanthemum coronarium L.): chlorogenic acid, 3,5-dicaffeoylquinic acid and 4-succinyl-3,5-dicaffeoylquinic acid, were investigated together with caffeic acid by Takenaka, M. et al as published in the Biosci Biotechnol Biochem 2000 Dec volume 64 titled "Stability and bioavailability of antioxidants in garland". These compounds were stable in artificial digestive juice, but more than 90% of them disappeared from plasma within 30 min after intravenous injection into rats. When they were orally administered, only caffeic acid could be detected. The data supports a higher level of bioavailability of chlorogenic acids through increased solubility and stability. From the coffee bean analysis depicted in Figures 1 – 3 it is clear that chlorogenic acid is the prominent pholyphenol in the extracts claimed in the present invention.

Although the invention has been described with reference to specific embodiments, this description is not meant to be construed in a limited sense. Various modifications of the disclosed embodiments, as well as alternative embodiments of the inventions will become apparent to persons skilled in the art upon the reference to the description of the invention. It is, therefore, contemplated that the appended claims will cover such modifications that fall within the scope of the invention.

I claim:

1. A method for producing a beneficial extract from raw coffee beans comprising the steps of:

selecting a measure of raw green coffee beans;

extracting beneficial compounds from said derivative raw green coffee beans.

2. The method of Claim 1 further comprising the step of processing said raw green coffee beans to produce derivative raw green coffee beans before said extracting.

3. An extract having beneficial compounds produced by a method comprising the steps of:

selecting a measure of raw green coffee beans;

extracting beneficial compounds from said derivative raw green coffee beans.

4. A method for enhancing the shelf life of perishable substances comprising the steps of:

producing an extract from raw green coffee beans;

applying an effective measure of said extract to said perishable substances.

5. A method for preventing the onset or proliferation of disease and age-related maladies comprising the steps of:

producing an extract from raw green coffee beans;

administering a therapeutic dose of said extract to a recipient.

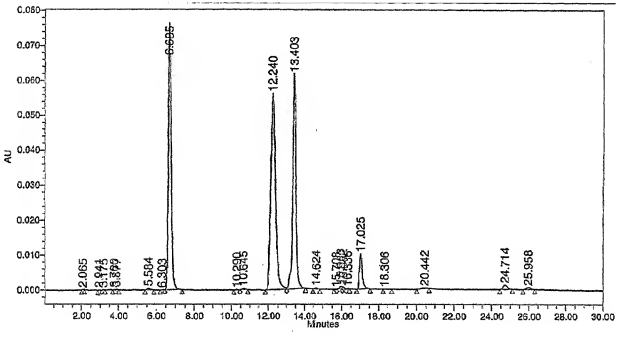
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Fig. 1

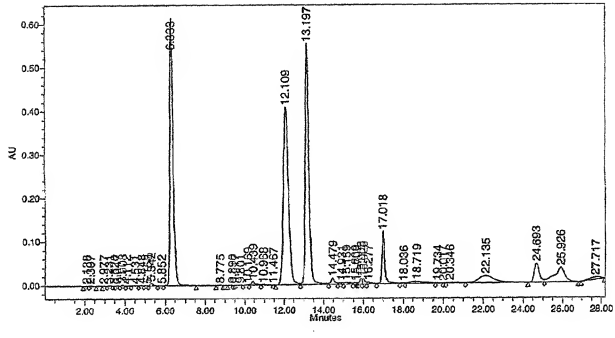
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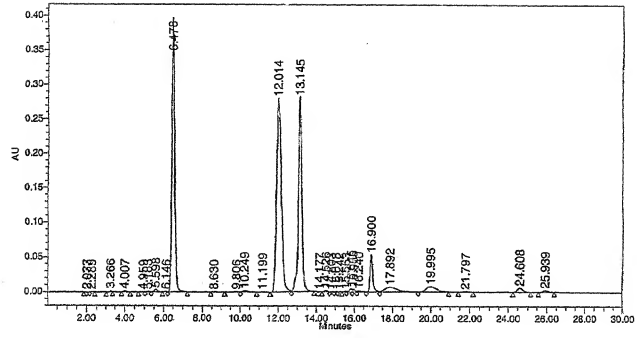
Fig. 2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24.00
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30.00
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3.266
4.007
4.959
5.598
6.146
6.479
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24.608
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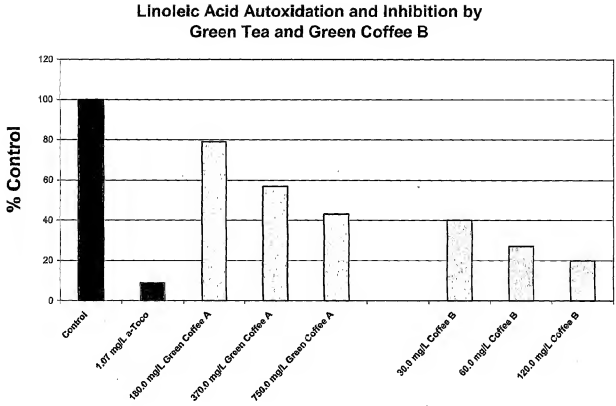
Fig. 3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120
100
80
60
40
20
0
Control
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370.0 mg/L Green Coffee A
750.0 mg/L Green Coffee A
30.0 mg/L Coffee B
60.0 mg/L Coffee B
120.0 mg/L Coffee B

Fig. 4

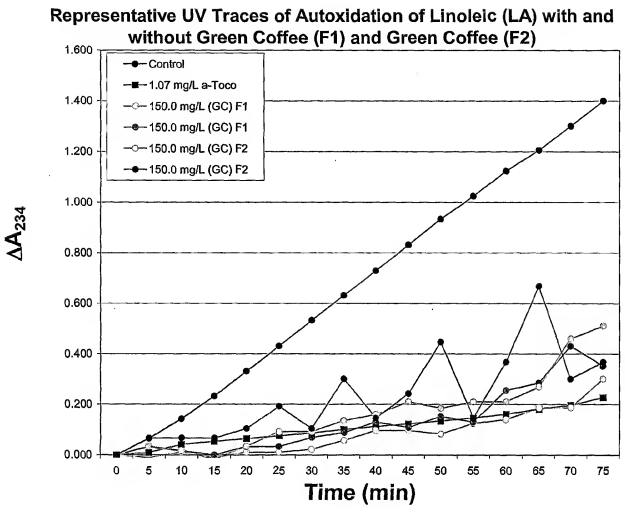
Representative UV Traces of Autoxidation of Linoleic (LA) with and without Green Coffee (F1) and Green Coffee (F2)
Control
1.07 mg/L a-Toco
150.0 mg/L (GC) F1
150.0 mg/L (GC) F1
150.0 mg/L (GC) F2
150.0 mg/L (GC) F2
ΔA234
1.600
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Time (min)

Fig. 5

Analysis	Example No			
Items	3A	3B	3C	3D
Coffee polyphenolic content* (mg/500ml):	0	340	980	460
Visible haze (at 4°C for 5 days):	++	±	-	-
Durability**:	6.0	3.0	1.5	2.0

*Polyphenol content, Measured by HPLC using chlorogenic acid as standard.

** Durability of beer

The beer contained in a bottle (can) was submerged in the water maintained at a constant temperature of 60±1°C in an erected manner for 72 hours, cooled with the water, submerged in a cooling bath maintained at 0°C for 24 hours, and was introduced into a cell of a turbidimeter to measure the turbidity at 0°C.

Fig. 6

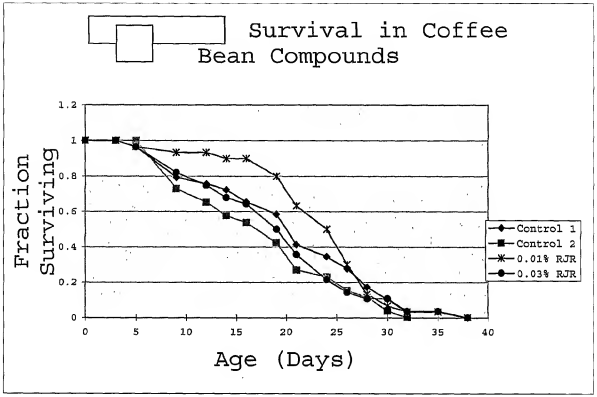
Survival in Coffee Bean Compounds
Fraction Surviving
1.2
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
40
Age (Days)
Control 1
Control 2
0.01% RJR
0.03% RJR

Fig. 7

Catechins (type)	Peak Plasma Conc in humans[A]	Plasma Concentration in rats[B]	Plasma Concentration in mice[C]
EGCG	120 ng/ml	37 ng/ml	124 ng/ml
EGC	148 ng/ml	55 ng/ml	62 ng/ml
EC	55 ng/ml	20 ng/ml	10 ng/ml
Total	323 ng/ml	57 ng/ml	196 ng/ml

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/12778

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 35/78
US CL : 424/725, 776
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/725, 776

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPT, PGPB, JPAB, EPAB, DWPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 4,883,651 A (MEYER) 28 November 1989 (28.11.1989), column 1, lines 60-65, column 2, lines 48-51.	1-3 --- 4
X --- Y	JP 04-145048 A (T HASEGAWA CO LTD.) 19 May 1992 (19.05.1992), see English abstract.	1-4 --- 5
X	JP 09-151319 A (HASEGAWA CO LTD. [HASE]) 11 June 1996 (11.06.1996), see English abstract.	1-3, 5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 May 2002 (28.05.2002)	28 JUN 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Susan Coe
Facsimile No. (703)305-3230	Telephone No. (703)308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/12778

Continuation of Item 4 of the first sheet:
The title is too long, PCT Rule 4.3. "THERAPEUTIC PREPARATION FROM COFFEE BEAN AND METHOD FOR PRODUCING"